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NEWSLETTER

ANTIPSYCHOTIC AGENTS

MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE

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ANTIPSYCHOTIC AGENTS

The current American Psychiatric Association practice guideline for the treatment of patients with schizophrenia recommends either typical or atypical antipsychotics as first line therapy for acute psychosis. Atypical antipsychotics cause fewer tardive dyskinesias and are more effective at improving negative schizophrenic symptoms such as avolition, anhedonia, and alogia. Due to their improved adverse effect profile, the atypical antipsychotics are often used as first-line therapy for the management of psychotic disorders. If the adverse effects of the typical antipsychotics are intolerable, patients should be switched to an atypical antipsychotic such as risperidone, quetiapine, or olanzapine. Although clozapine is an atypical antipsychotic, the American Psychiatric Association recommends that it be reserved for patients who are refractory to previous antipsychotic treatments as clozapine treatment requires weekly blood monitoring due to the potential for severe leukopenia.[1-3] Typical anti-psychotics may be used in combination with atypical antipsychotics when patients demonstrate an inadequate response to monotherapy.

Typical antipsychotics are divided into several classes, the phenothiazines, thioxanthines, phenylbutylpiperadines, dihydroindolones and dibenzepines. These agents are described as having "high" or "low" potency. As a class, the typical antipsychotics are equally effective at improving schizophrenic symptoms when used in equipotent doses. High potency agents cause more extrapyramidal and parkinsonian adverse effects such as tremor, akathisia, akinesia, rigidity, and acute dystonias. Low potency agents generally cause more sedation, hypotension, and anticholinergic effects than high potency agents, although extrapyramidal and parkinsonian adverse effects also occur. Antipsychotic agents may also cause chronic extrapyramidal adverse effects occurring months to years after treatment. Chronic effects may not resolve upon discontinuation of therapy. Anticholinergic effects such as dry mouth, blurred vision, constipation, tachycardia, and urinary retention may be intolerable to many patients. Extrapyramidal and parkinsonian adverse effects may be treated with anticholinergic agents such as benztropine, however this may lead to serious or life-threatening anticholinergic toxicities such as ileus, hyperthermia, impaired cognition and memory, confusion, delirium, somnolence, and hallucinations. Elderly patients are more susceptible to the extrapyramidal, parkinsonian, and anticholinergic adverse effects of the typical antipsychotics.[1-3] The typical antipsychotics available for use are chlorpromazine, fluphenazine, mesoridazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, thiothixine, haloperidol, pimozide, molindone, and loxapine. Haloperidol and fluphenazine are available for depot therapy and may be administered every 2-4 weeks. Depot formulations of the typical antipsychotics have the same adverse effect profile as the oral formulations.[1-3]

Atypical antipsychotic medications are loosely

described as those agents that are able to effectively treat psychotic symptoms without causing the extrapyramidal side effects associated with the standard antipsychotic agents. They have demonstrated superior efficacy in treating the negative symptoms of schizophrenia such as alogia, avolition, and anhedonia. Due to these significant benefits, the atypical antipsychotic agents are increasingly being used as first-line therapy for the management of the manifestations of psychotic disorders. The four medications available for use include clozapine, olanzapine, quetiapine, and risperidone.

1. Maximum usual dosage:

Table 1 contains usual dosage ranges and approximate equivalent doses for the typical antipsychotics; maximum doses are presented when available. An adequate dose of a typical antipsychotic is the most effective dose that causes the fewest side effects. Initial doses generally fall into the range of 300 – 1000 mg of chlorpromazine, while maintenance doses generally range from 300 – 600 mg of chlorpromazine.

Monitor patients for efficacy, adverse effects such as extrapyramidal effects, anticholinergic effects, tardive dyskinesias, and compliance over the initial 3 weeks of therapy. Response is generally seen after 4-6 weeks at an adequate dose. Little evidence supports high doses at initiation of therapy. Assess non-compliant patients for adverse effects, as they may not be able to tolerate the typical antipsychotics. Atypical antipsychotics represent a good option for patients who cannot tolerate the adverse effects of the typical antipsychotics or require many additional treatments to counteract adverse effects. If non-compliance is due to forgetfulness or dislike of a daily medication, these patients may be candidates for depot therapy. Doses for elderly patients are generally lower and must be titrated slowly as these patients are more susceptible to the adverse effects of typical antipsychotics.[1-3, 5]

Usual and maximum adult doses for the atypical antipsychotics are listed in Table 2. In elderly patients, atypical antipsychotics have been shown to provide relief of delirium, delusions, and other psychotic disorders of late life with fewer adverse effects than are commonly seen with standard antipsychotic medications. Dosing may be started as low as one-third to one-half the normal starting dose and titrated slowly to the desired effect so as to minimized adverse effects. Elderly patients rarely tolerate or require the doses used in healthy adults. Small clinical trials of atypical antipsychotic medication use in children with autism and various mood disorders have been conducted. Safety and efficacy in pediatric patients have not been established for any of the atypical antipsychotic medications

2. Indication for use

The typical antipsychotics have many indications beyond the management of psychotic disorders including nausea and vomiting. This review will address the use of these agents in managing the manifestations of psychotic disorders.[6]

Olanzapine, quetiapine, and risperidone are indicated for the management of the manifestations of psychotic disorders. Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond to standard antipsychotic drug treatment.

Duration of therapy

Exact duration of antipsychotic therapy is not clear. Patients should receive at least one year of therapy after establishing an effective dose with tolerable side effects. Review patient's need for medication and assess adverse effects periodically. Many patients require indefinite treatment.[2, 4]

Duplicative therapy

No evidence supports the use of multiple typical or atypical antipsychotic agents. Titrate patients to the minimum effective dose with the fewest adverse effects. Reasonable trials of monotherapy should be attempted in all patients. The combination of an atypical and typical agent is

an option for patients who do not respond to monotherapy.[2, 4] *Some patients may experience breakthrough of positive symptoms or report subjective worsening of symptoms in the absence of combination therapy.*

Drug-drug interactions

Routine study of drug interactions is a recent requirement in the drug approval process. Significant drug interactions have been identified with both typical and atypical antipsychotics. The following list describes some clinically significant drug-drug interactions with the typical and atypical antipsychotics. Lack of space prohibits a more detailed description. Additional detailed information is available in other sources. [7-10]

Agents that prolong the QT interval – Typical antipsychotics may prolong the QT interval. When combined with other agents such as **amiodarone**, **cisapride**, **sparfloxacin**, and **tricyclic antidepressants**, additive QT interval prolongation may result in life threatening cardiac arrhythmias.

Anticholinergic agents – Anticholinergic agents such as **benztropine** or **antihistamines** such as **diphenhydramine** are often used in combination with typical antipsychotics to manage significant tardive dyskinesic adverse effects. However, these agents may potentiate the significant anticholinergic effects of the typical antipsychotics resulting in potentially fatal anticholinergic toxicity.

Anticonvulsant agents – Combinations of typical antipsychotics and anticonvulsants such as **carbamazepine**, **phenytoin**, or **phenobarbital** may result in altered blood levels of either agent. When initiating or discontinuing therapy with either agent it is essential to monitor efficacy and toxicity of both agents. **Carbamazepine** may induce the metabolism of **clozapine**, **olanzapine**, **quetiapine**, and **risperidone** decreasing their efficacy. Neuroleptic malignant syndrome has been reported with concomitant use of carbamazepine and clozapine. **Fosphenytoin** and **phenytoin** may induce the metabolism of clozapine decreasing its efficacy. **Phenytoin** has been shown to markedly increase the clearance of quetiapine; clinical relevance is inferred.

Macrolide antibiotics - Clarithromycin, **erythromycin**, and **troleandomycin** may inhibit the metabolism of **clozapine** causing an increased potential for adverse effects due to clozapine. **Azithromycin** and **dirithromycin** should not impact **clozapine** metabolism significantly.

a. Ritonavir - Ritonavir may interfere with the metabolism of **clozapine** causing an increased potential for adverse effects due to clozapine.

Potential cytochrome P450 interactions – Metabolism through the cytochrome P450 system is not established for many antipsychotics. **Haloperidol** and **olanzapine** are substrates of CYP1A2. Inducers of this enzyme such as **phenobarbital** or **rifampin** may decrease concentrations of these agents. Inhibitors of this enzyme such as **propranolol** or **erythromycin** may increase concentrations. **Haloperidol**, **perphenazine** and **thioridazine** are inhibitors as well as substrates of the CYP2D6 system. CYP2D6 is a minor metabolizer of olanzapine and does not seem to significantly impact its elimination. The CYP2D6 system is not affected by common inducers, but may be inhibited by drugs such as **amiodarone**, **fluoxetine**, **paroxetine**, and **sertraline**. **Chlorpromazine** and **quietapine** are substrates of the CYP3A4 system. Inhibitors of this system such as **erythromycin**, **ketoconazole**, or **cimetidine** may increase concentrations of these agents. Inducers of this system such as **carbamazepine**, **phenobarbital**, **phenytoin** or **rifampin** may decrease concentrations.

Table 1. Typical antipsychotics - usual and maximum dosage

Drug	Dosage form(s)	Equivalent dose (mg)	Usual Acute Dose	Usual Maintenance Dose	Maximum Daily dose
Phenothiazines					
Chlorpromazine (Thorazine)	Tablets: 10, 25, 50, 100, 200 mg Oral solution: 30 mg/mL, 100 mg/mL	100	200-1000	50-600	None reported
Fluphenazine HCl (Prolixin, Permitil)	Tablets: 1, 2.5, 5, 10 mg Oral solution: 5 mg/mL	2	5-50	1-15	No safety data on prolonged doses > 40 mg/day
Fluphenazine decanoate (PMS-Fluphenazine, Modecate, Rhohenazine)	Decanoate injection: 25 mg/mL	N/A	N/A	12.5-100 mg	No safety data on doses > 100 mg
Mesoridazine (Serentil)	Tablets Oral solution	50	100-400	30-400	None reported
Perphenazine (Trilafon)	Tablets: 2, 4, 8, 16 mg Oral solution: 16 mg/5mL	10	12-100	12-64	None reported
Prochlorperazine (Compazine)	Tablets: 5, 10 mg Spansule: 10, 15 mg Oral solution: 1 mg/mL	15	50-200	50-200	None reported
Thioridazine (Mellaril)	Tablets: 10, 15, 25, 50, 100, 150, 200 mg Oral solution: 30 mg/mL, 100 mg/mL	100	200-800	200-800	None reported
Trifluoperazine (Stelazine)	Tablets: 1,2,5,10, mg Oral solution: 10 mg/mL	5	10-60	4-30	None reported
Thioxanthenes					
Thiothixene (Navane)	Capsules: 1, 2, 5, 10, 20 mg Oral solution: 5 mg/mL	5	10-60	6-30	No additional benefit for doses > 60 mg/day
Phenylbutylpiperadines					
Haloperidol (Haldol)	Tablets: 0.5, 1, 2, 5, 10, 20 mg Oral solution: 2 mg/mL	2	5-50	1-15	No additional benefit for doses > 100 mg/day
Haloperidol decanoate (Haldol Decanoate, Haloperidol LA)	Decanoate injection 50 mg/mL, 100 mg/mL	N/A	N/A	10-15 x oral dose	None reported
Pimozide (Orap)	Tablets: 2 mg	0.3-0.5	1-10	1-10	None reported
Dihydroindolones					None reported
Molindone (Moban, Lidone)	Tablets: 5, 10, 25, 50, 100 mg Oral solution: 20 mg/mL	10	40-225	15-100	None reported
Dibenzepine					None reported
Loxapine (Loxitane)	Capsules: 10, 50 mg	10	20-160	10-60	Doses should not exceed 250 mg/day

Table 2. Aypical antipsychotics - usual and maximum dosage

Drug	**Ingredient(s)**	***Usual Dose***	***Maximum Daily Dose***
Clozapine (Clozaril)	Clozapine 25 mg and 100 mg tablets	Initiate therapy at 25 mg QD or BID then increase by 25 mg to 50 mg daily over 2 weeks to a target daily dose of 300 – 450 mg. Administer in divided doses as tolerated.	Dosing should not exceed 900 mg/day.
Olanzapine (Zyprexa)	Olanzapine 5 mg, 7.5 mg, and 10 mg tablets	Initiate therapy at 5 mg or 10 mg QD. Dosage adjustments of 5 mg QD are recommended after clinical evaluation and at least one week of any previous dose change.	Safety has not been assessed at doses greater than 20 mg/day.
Quetiapine (Seroquel)	Quetiapine 25 mg, 100 mg, and 200 mg tablets	Initiate therapy at 25 mg BID and increase by 25 mg to 50 mg BID on days two, tree, and four to a daily dose range of 300 mg to 400 mg. Maximum clinical effect occurred at 300 mg/day in dose-response studies.	Safety has not been assessed at doses greater than 800 g/day.
Risperidone (Risperdal)	Risperidone 1 mg, 2 mg, 3 mg, and 4 mg tablets	Initiate therapy at 1 mg BID and increase by 1 mg BID on days two and three of treatment to a target dose of 3 mg BID. Dose adjustment may then occur no sooner than one week after a previous change. Maximum efficacy has been noted at doses between 4 and 6 mg/day. Doses up to 16 mg/day have been used.	Safety has not been assessed at doses higher than 16 mg per day.

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